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10/534,348

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Karen Silence

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EXAMINER

EMCH, GREGORY S

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/534,348	<b>Applicant(s)</b> SILENCE ET AL.	
	<b>Examiner</b> Gregory S. Emch	<b>Art Unit</b> 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 03 March 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-13, 15-21, 26, 28, 38-41 and 44-48 is/are pending in the application.
- 4a) Of the above claim(s) 9, 11, 13, 17-20, 26, 28, 38, 39, 41 and 44-48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8, 10, 12, 15, 16, 21 and 40 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 May 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |  |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)                              |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____   |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application                    |
| Paper No(s)/Mail Date <u>See Continuation Sheet</u> .                                  | 6) <input checked="" type="checkbox"/> Other: <u>Sequence alignments A, B and C.</u> |

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :09/11/06; 12/14/06; 06/11/07; 08/09/07; 04/14/08; 04/28/08; 10/28/08.

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicants' election with traverse of Group VI, claims 1-13, 15, 16, 21 and 40 drawn to anti-TNF-alpha polypeptides to the extent of SEQ ID NO: 35, in the reply filed on 03 March 2008 is acknowledged. The traversal is on the ground(s) that, "Applicant traverses the requirement to elect a single sequence. The election of the sequence is made with traverse because certain claims are directed to polypeptides comprising at least one anti-TNF-alpha single domain antibody, which do not require another single domain antibody. Therefore, it is improper to require Applicant to select a sequence from among only SEQ ID NOs: 30-43 and 73-76, which are all sequences of polypeptides that include more than one single domain antibody. Based on the undersigned's conversation with the Examiner, noted above, Applicant elects herewith three sequences. As an anti-TNF-alpha single domain antibody sequence, Applicant elects SEQ ID NO: 1. As a sequence of a single domain antibody directed against a serum protein, Applicant elects SEQ ID NO: 28. As a sequence that comprises an anti-TNF-alpha single domain antibody sequence and a sequence of a single domain antibody directed against a serum protein, Applicant elects SEQ ID NO: 35."

Applicants' arguments have been fully considered and are found persuasive. The elected claims of Group VI set forth above will be examined to the extent of SEQ ID NOs: 1, 28 and 35.

Claims 1-13, 15-21, 26, 28, 38-41 and 44-48 are pending in the instant application.

Claims 9, 11, 13, 17-20, 26, 28, 38, 39, 41 and 44-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03 March 2008.

Claims 1-8, 10, 12, 15, 16, 21 and 40 are under examination in the instant office action.

### ***Information Disclosure Statements***

Signed and initialed copies of the IDS papers filed on 11 September 2006, 14 December 2006, 11 June 2007, 09 August 2007, 14 April 2008, 28 April 2008 and 28 October 2008 are enclosed in this action.

### ***Claim Objections***

Claim 1 is objected to because of the following informalities: The claim does not define the acronym TNF-alpha at its first mention. It is suggested that "tumor necrosis factor-alpha" is added directly before "TNF-alpha" in claim 1, line 1.

Claim 2 is objected to because of the following informalities: The claim recites "An anti-TNF-alpha polypeptide according to claim 1 wherein a single domain antibody...." It is suggested that this claim be amended to recite "An anti-TNF-alpha

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polypeptide according to claim 1 wherein the at least one single domain antibody...“ to have proper antecedent basis.

Claim 5 is objected to because of the following informalities: The claim contains a typo, i.e. “wherein the anti-single domain antibody correspond” (see line 2). This phrase does not contain proper subject-verb agreement.

Claim 7 is objected to because of the following informalities: The claim does not define the acronym IFN-gamma at its first mention. It is suggested that “interferon-gamma” is added directly before “IFN-gamma” in claim 7, line 3.

Claim 11 is objected to because of the following informalities: The claim does not define the acronym VHH at its first mention. It is suggested that “variable domain derived from a heavy chain antibody devoid of light chains” is added directly before “VHHs” in claim 10, line 2.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

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be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 10, 12, 15, 16, 21 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 44, 47 and 66 of copending Application No. 10/534,349. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '349 application are drawn to a polypeptide construct comprising: at least one single domain antibody directed against a therapeutic and/or diagnostic target, and at least one single domain antibody directed against a serum protein, (and compositions thereof), including wherein the therapeutic or diagnostic target is TNF-alpha and wherein the single domain antibodies are humanized *Camelidae* VHH antibodies, as in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-8, 10, 12, 15, 16, 21 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15, 22, 25-39 and 46 of copending Application No. 11/788,832. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '832 application are drawn to an anti-TNF-alpha polypeptide comprising one or more single domain antibodies directed against TNF-alpha and an Fc domain

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(and compositions thereof), and wherein the single domain antibodies are humanized *Camelidae* VHH antibodies, as in the instant claims. Moreover, claims 12-15 and 36-39 of the '832 application are drawn to an anti-TNF polypeptide comprising SEQ ID NO: 1, in which SEQ ID NO: 1 is identical to the instant elected sequence of SEQ ID NO: 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-8, 10, 12, 15, 16, 21 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 11, 22, 24, 25, 27 and 30-33 of copending Application No. 11/804,647. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 10 and 11 of the '647 application are drawn to a polypeptide comprising an anti-human TNF-alpha single domain antibody (dAb) and an anti-serum albumin (SA) dAb, and wherein the dAbs are Camelid VHH domains, as in the instant claims. Claims 22, 24, 25, 27 and 31-33 of the '647 application are drawn to a polypeptide comprising a first immunoglobulin single variable domain having binding specificity for serum albumin (SA), and a second immunoglobulin single variable domain having binding specificity for an antigen, including TNF-alpha, as in the instant claims. Claim 30-33 are also drawn to a polypeptide comprising (i) first and second heavy chain single variable domains, or (ii) first and second light chain single variable domains, wherein each domain has binding specificity to an antigen including TNF-alpha, as in the instant claims.



This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 15 and 16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims, as written, do not sufficiently distinguish the claimed invention over proteins that exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. It is noted that the instant specification defines a "single domain antibody" as one that "is a naturally occurring single domain antibody known as heavy chain devoid of light chains (WO 9404678)" (see p.4, lines 13-15). Thus, claims 1, 2, 15 and 16 encompass naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor by insertion of "isolated" or "purified," for example. See MPEP 2105.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The claim is directed to a composition comprising an anti-TNF-alpha polypeptide according to claim 1 and at least one single domain antibody from the group consisting of anti-IFN-gamma single domain antibody, anti-TNF-alpha receptor single domain antibody and anti-IFN-gamma receptor single domain antibody, for simultaneous, separate or sequential administration to a subject.

It is unclear how a composition that comprises both an anti-TNF-alpha polypeptide and at least one single domain antibody as set forth above can be administered separately or sequentially. That is, if the composition comprises both components, how can the two components be administered other than by simultaneous administration? Clarification is required.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 15, 21 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 91/02078A1 to Rathjen et al. (citation B5 on IDS dated 11 September 2006).

Claim 1 is directed to an anti-TNF-alpha polypeptide comprising at least one anti TNF-alpha single domain antibody. Claim 15 is directed to the anti-TNF-alpha polypeptide according to claim 1, wherein the anti-TNF-alpha polypeptide is an homologous sequence, a functional portion, or a functional portion of an homologous sequence of the full length anti-TNF-alpha polypeptide. Claim 21 is directed to a kit for screening for agents that modulate Tumor Necrosis Factor-alpha-mediated disorders comprising an anti-TNF-alpha polypeptide of claim 1 and Tumor Necrosis Factor-alpha. Claim 40 is directed to a composition comprising the anti-TNF-alpha polypeptide of claim 1 and a suitable pharmaceutical vehicle.

WO 91/02078A1 to Rathjen et al. teaches polypeptide ligands that bind to TNF-alpha and alter its biological activity, including single domain antibodies and polypeptides which are synthetic and analogous (i.e. homologous) to the ligands that bind to TNF (see abstract and p.4, lines 20), thus meeting the limitations of claim 1 and 15. The Rathjen et al. reference teaches a composition comprising TNF-alpha and the ligand that binds to TNF, (e.g. a TNF-alpha single domain antibody), thus meeting the limitations of claim 21. Although the patent does not explicitly recite the claimed "kit," this limitation, i.e. "a kit for screening for agents that modulate Tumor Necrosis Factor-alpha mediated disorder" is recited in the preamble of claim 21 and is thus given no patentable weight (see MPEP § 2111.02, II). Thus, the Rathjen et al.'s disclosure of the products immediately set forth above is deemed to meet the limitations of claim 21. The Rathjen et al. reference teaches the antibodies of the invention contained in pharmaceutically acceptable vehicles, e.g. phosphate buffered saline (p.19, line 25),

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thus meeting the limitations of claim 40. Since the reference teaches all the elements of the claims, claims 1, 15, 21 and 40 are anticipated by Rathjen et al.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 3 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,670,453 to Frenken et al. (priority date of 27 October 1998).

Claims 1 and 3 are directed to an anti-TNF polypeptide comprising at least one anti-TNF-alpha single domain antibody (claim 1), further comprising at least one single domain antibody directed against a serum protein (claim 3). Claim 6 is directed to the anti-TNF polypeptide according to claim 3, wherein the anti-TNF polypeptide corresponds to a sequence represented by any of the elected sequence of SEQ ID NO: 35.

U.S. Patent No. 6,670,453 to Frenken et al. teaches a multivalent antigen binding protein comprising a single polypeptide chain comprising, connected in series, two or more single domain binding units (col.1, lines 12-15) and teaches a polypeptide

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corresponding to a sequence represented by SEQ ID NO: 35 (see attached sequence alignment A). It is noted that the claimed language of “corresponding to a sequence represented by any of” SEQ ID NO: 35 encompasses short fragments of SEQ ID NO: 35 (i.e. polypeptides with less than 100% identity to SEQ ID NO: 35), which are taught by the Frenken et al. patent, as shown in the attached sequence alignment. The Frenken et al. patent does not explicitly recite that the polypeptides disclosed therein comprise a TNF single domain antibody (as encompassed by claim 1), further comprising at least one single domain antibody directed against a serum protein (as encompassed by claims 3 and 6). However, because the patent teaches “a sequence represented by any of” SEQ ID NO: 35, the patent inherently teaches the remaining limitations of claims 1, 3 and 6. Applicants are reminded that chemical compounds and their properties are inseparable (In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA1963)), as are their processes and yields (In re Von Schickh, 362 F.2d 821, 150 USPQ 300 (CCPA 1966)). Thus, absent evidence to the contrary, the Frenken et al. patent inherently teaches the limitations of claims 1, 3 and 6, since it teaches a polypeptide corresponding to a sequence represented by SEQ ID NO: 35.

It is noted that amending dependent claim 6 to recite “An anti-TNF-alpha polypeptide according to claim 3, comprising the amino acid sequence of SEQ ID NO: 35” would be remedial in overcoming the instant rejection.

***Claim Rejections - 35 USC § 103***

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, 7, 8, 12 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,759,518 to Kontermann et al. (priority date of 09 April 1999; citation A3 on IDS dated 11 September 2006).

The claims are directed to an anti-TNF-alpha polypeptide comprising at least one anti-TNF-alpha single domain antibody.

The Kontermann et al. patent teaches polypeptide constructs comprising at least one or at least two single domain antibodies with at least two specificities, including a therapeutic and/or diagnostic target (col.3, lines 31-45). The Kontermann et al. patent teaches that therapeutic targets for the single domain antibodies can be cytokines, such as TNF-alpha and IFN-gamma (col.7, line 18; col.14, line 55) and that another specificity can be serum albumin (col.16, line 18), as in the instant claims 1, 3, 4, 7 and 12. The patent teaches an example of a polypeptide construct, which has 4 single domains, 2 with a first specificity and 2 with a second specificity (col.3, lines 31-45), as in the instant claim 8. The patent teaches pharmaceutical compositions comprising the polypeptides (col.9, lines 59-65), as in the instant claims 12 and 40.

The difference between the claimed invention and those of the Kontermann et al. patent is that said patent does not specifically teach a particular polypeptide construct with at least one single domain antibody directed against TNF-alpha and one directed against serum albumin or a particular construct with at least one single domain antibody directed against TNF-alpha and one directed against IFN-gamma. However, upon reading the disclosure of the Kontermann et al. patent, the skilled artisan would have recognized the desirability of developing constructs with these characteristics. Furthermore, it would have been reasonable to predict that said constructs could be successfully generated and used in methods of treatment and/or diagnosis. Thus, it would have been obvious to the person of ordinary skill in the art at the time the

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invention was made to use Kontermann et al.'s disclosure to produce the claimed constructs to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to a combination of equivalent elements to obtain predictable results.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,759,518 to Kontermann et al. as applied to claims 1, 3, 4, 7, 8, 12 and 40 above, and further in view of U.S. Patent No. 7,368,111 to Thompson et al. (priority date of 07 October 1996).

The Kontermann et al. patent teaches as set forth above and additionally teaches that a therapeutic target for the single domain antibodies can be transforming growth factor-beta (TGF $\beta$ ), including isoforms TGF $\beta$ 1 and TGF $\beta$ 2 (cols.14-15).

The difference between the claimed invention and the disclosure of the Kontermann et al. patent is that said patent does not specifically teach a particular polypeptide construct with at least one single domain antibody directed against TNF-alpha and wherein a single domain antibody corresponds to a sequence represented by any of the elected sequence of SEQ ID NO: 1. However, upon reading the disclosure of the Kontermann et al. patent, the skilled artisan would have recognized the desirability of developing a construct with at least one single domain antibody directed against TNF-alpha and with at least one single domain antibody directed against TGF $\beta$ . Furthermore, U.S. Patent No. 7,368,111 to Thompson et al. teaches antibodies to TGF-



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beta, including one that corresponds to a sequence represented by SEQ ID NO: 1 (see attached Sequence alignment B), as in the instant claim 2. It is noted that the claimed language of "corresponds to a sequence represented by any of" SEQ ID NO: 1 encompasses short fragments of SEQ ID NO: 1, which are taught by the Thompson et al. patent, as shown in the attached sequence alignment. It would have been reasonable to predict that a protein construct with a single domain antibody directed against TNF-alpha and a single domain antibody directed against TGFβ could be successfully generated and used in methods of treatment and/or diagnosis. Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to improve Kontermann et al.'s disclosure to produce the claimed polypeptide as taught by Thompson et al. to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to a combination of equivalent elements to obtain predictable results.

It is noted that amending claim 2 to recite "An anti-TNF-alpha polypeptide according to claim 1, comprising the amino acid sequence of SEQ ID NO: 1" would be remedial in overcoming the instant rejection.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,759,518 to Kontermann et al. as applied to claims 1, 3, 4, 7, 8, 12 and 40 above, and further in view of U.S. Patent No. 7,084,257 to Deshpande et al. (priority date of 05 October 2001).

The Kontermann et al. patent teaches as set forth above. The difference between the claimed invention and the disclosure of the Kontermann et al. patent is that said patent does not specifically teach a particular polypeptide construct with at least one single domain antibody directed against TNF-alpha and wherein a single domain antibody corresponds to a sequence represented by any of the elected sequence of SEQ ID NO: 28. However, upon reading the disclosure of the Kontermann et al. patent, the skilled artisan would have recognized the desirability of developing a construct with at least one single domain antibody directed against TNF-alpha and with at least one single domain antibody directed against one directed against IFN-gamma.

Furthermore, 7,084,257 to Deshpande et al. teaches antibodies and single domain antibodies to IFN-gamma, including one that corresponds to a sequence represented by SEQ ID NO: 28 (see co.2 and attached Sequence alignment C), as in the instant claim 5. It is noted that the claimed language of "corresponds to a sequence represented by any of" SEQ ID NO: 28 encompasses short fragments of SEQ ID NO: 28, which are taught by the Deshpande et al. patent, as shown in the attached sequence alignment. It would have been reasonable to predict that a protein construct with a single domain antibody directed against TNF-alpha and a single domain antibody directed against IFN-gamma could be successfully generated and used in methods of treatment and/or diagnosis. Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to improve Kontermann et al.'s disclosure to produce the claimed polypeptide as taught by Deshpande et al. to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her

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technical grasp to obtain predictable results. Such would amount to a combination of equivalent elements to obtain predictable results.

It is noted that amending claim 5 to recite "An anti-TNF-alpha polypeptide according to claim 3, wherein the anti-serum protein single domain antibody comprises the amino acid sequence of SEQ ID NO: 28" would be remedial in overcoming the instant rejection.

Claims 10 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,759,518 to Kontermann et al. as applied to claims 1, 3, 4, 7, 8, 12 and 40 above, and further in view of EP 584421 A1 to Casterman et al. (citation B26 on IDS dated 28 October 2008).

The Kontermann et al. patent teaches as set forth above but fails to teach that the single domain antibodies can be Camelidae heavy chain antibodies. However, upon reading the disclosure of the Kontermann et al. patent, the skilled artisan would have recognized the desirability of developing protein constructs that are less immunogenic for human use. Furthermore, EP 584421 A1 to Casterman et al. teaches that heavy chain single domain antibodies from camelids are desirable and teaches that these antibodies can be humanized, and thus would be less immunogenic for human use (entire document, e.g. p.3, lines 35-57), as in claims 10 and 16. As evidenced by the prior art, the skilled artisan would have known that developing alternative protein constructs for treatment or diagnosis of humans would be desirable. Furthermore, it would have been reasonable to predict that humanized camelidae heavy chain

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antibodies could be successfully incorporated into the constructs of Kontermann et al.

Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to improve Kontermann et al.'s single domain antibody constructs as disclosed by Casterman et al. to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to a simple substitution of known equivalents to obtain predictable results.

### ***Conclusion***

No claims are allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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